PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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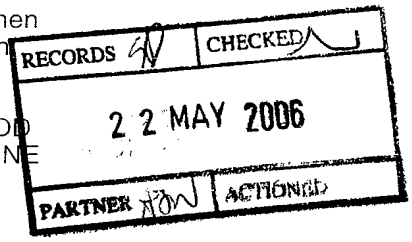

PCT

WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rule 66)

Date of mailing *(day/month/year)*	18.05.2006
Applicant's or agent's file reference ATHCZ/P32969PC	**REPLY DUE** within 1 month(s) from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/001451	15.04.2005	15.04.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K38/17 A61K39/395 A61P7/02

Applicant
ATHERA BIOTECHNOLOGIES AB et al.

1. ☐ The written opinion established by the International Searching Authority:
   ☐ is ☒ is not
   considered to be a written opinion of the International Preliminary Examining Authority.

2. This first opinion contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

   When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(e).
   How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.
   Also: For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*. For an informal communication with the examiner, see Rule 66.6. For an additional opportunity to submit amendments, see Rule 66.4.
   If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary report on patentability (Chapter II of the PCT) must be established according to Rule 69.2 is: 15.08.2006

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Böhmerova, E Telephone No. +49 89 2399-7859

WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

International application No.
PCT/GB2005/001451

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into ,
   which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this opinion has been established on the basis of *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-17	as originally filed

Claims, Numbers

1-9	received on 02.02.2006 with letter of 01.02.2006

Drawings, Sheets

1/5-5/5	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

International application No.
PCT/GB2005/001451

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non- obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 4,5,8,9

because:

☒ the said international application, or the said claims Nos. 4,5,8,9 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search opinion has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See supplemental sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

International application No.
PCT/GB2005/001451

Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-9
Inventive step (IS)	Claims	1-9
Industrial applicability (IA)	Claims	1-3,6,7

2. Citations and explanations:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 4,5,8,9 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Cited documents

Reference is made to the following documents:

D1: US 2003/152513 A1 (BLANKENBERG FRANCIS G ET AL) 14 August 2003

D2: WO 02/067857 A (SURROMED, INC) 6 September 2002

D3: MARI C ET AL: "Annexin V, a new therapeutic tool in atherosclerosis" JOURNAL OF NUCLEAR MEDICINE, vol. 43, no. 5 Supplement, May 2002, page 7P, XP009051427 & 49TH ANNUAL MEETING OF THE SOCIETY OF NUCLEAR MEDICINE; LOS ANGELES, CA, USA; JUNE 15-19, 2002

D4: THIAGARAJAN PERUMAL ET AL: "Inhibition of arterial thrombosis by recombinant annexin V in a rabbit carotid artery injury model" CIRCULATION, [Online] vol. 96, no. 7, 1997, pages 2339-2347, XP002338645

D5: US 2003/170241 A1 (AUKRUST PAL ET AL) 11 September 2003

D6: SHERER Y ET AL: "Immunomodulation for treatment and prevention of atherosclerosis" AUTOIMMUNITY REVIEWS 2002 NETHERLANDS, vol. 1, no. 1-2, 2002, pages 21-27, XP002338646

D7: ALVES J D ET AL: "Atherosclerosis, oxidative stress and auto-antibodies in systemic lupus erythematosus and primary antiphospholipid syndrome" IMMUNOBIOLOGY, FISCHER, STUTTGART, DE, vol. 207, no. 1, 2003, pages 23-28, XP004954257

D8: GOLDENBERG H B ET AL: "Human antibody to phosphorylcholine is bactericidal against Haemophilus influenzae." ABSTRACTS OF THE GENERAL MEETING OF

THE AMERICAN SOCIETY FOR MICROBIOLOGY, vol. 103, 2003, pages D-116, XP009051386 & 103RD AMERICAN SOCIETY FOR MICROBIOLOGY GENERAL MEETING; WASHINGTON, DC, USA; MAY 18-22, 2003

Unless indicated otherwise reference is made to the passages considered relevant in the search report.

The documents D9-D11 were not cited in the international search report./Copies of the documents are appended hereto.

D9: Database Dissertation Abstract (online) ProQuest Info, Learning; 2002, Binder, Christoph, Johannes: "Defining innate and adaptive immune mechanisms in the atheroprotective effect of immunization with oxidized low-density lipoproteins", Database accession No. AADAA-I3064459

D10: Binder, Cristoph J. ET AL.., Nature Medicine, Vol 9, No. 6, June 2003, pages 736-743

D11: Rose N. ET. AL., Nature Medicine, vol 9, No. 6, 1 June 2003, pages 641-642

Novelty and inventive step

Claims 1-5 (Annexin V for preventing atherothrombosis and/or plaque rupture; method of treating a subject at risk of atherothrombosis and/or plaque rupture)

The applicant's arguments put forward in his letter dated 02.02.2006 have been taken into consideration, however the subject-matter of claims 1-4 is still considered to lack novelty in terms of 33(1) and (2) PCT, the reasons being as follows: document D1 relies on the use of annexin V coupled to a radioisotope and/or an effector molecule for detection and treatment of unstable (vulnerable) plaque. It can be admitted that the complex pf annexin V, a radioisotope and/or an effector molecule as claimed in D1 does not fall within the scope of present claims. However, D1 further teaches that 'the intrinsic anti-apoptic properties of internalized annexin V could also be exploited whereby radiolabelled annexin V for imagining could be co-injected with much greater amounts of unlabelled annexin V for therapeutic effect' (paragraph 31) and that 'the annexin is believed to both provide

binding and provide a therapeutic benefit when bound to the apoptotic or stressed cells characteristic of vulnerable plaque' (paragraph 33). Thus, besides the disclosure of the use of annexin V to target vulnerable plaque, D1 implicitly discloses the use thereof for therapeutic purposes, i.e. to treat vulnerable plaque. This disclosure is considered to anticipate novelty of claims 1-4.

Furthermore, claims 1-4 are considered to lack an inventive step under Art. 33(1) and (3) PCT as being obvious over D3 directly proposing annexin V as a suitable plaque stabilizer in vivo ('Annexin V may be useful as a stabilizer of atherosclerotic plaques, becoming a new tool in atherosclerosis treatment'). Stabilisation of atherosclerotic plaques is considered to be identical to the prevention of plaque rupture. This view is supported by the description of the present application stating that the present invention has shown that Annexin V may stabilize atherosclerotic plaque (page 2, lines 15-16).

The choice of systemic lupus erythematosus (SEE) patients (claim 5) cannot render the claimed subject matter inventive as atherosclerosis and coronary artery disease are known in the prior art as the major SEE complications - see D7.

Claims 6,8 (purified subfraction of pooled immunoglobulin to prevent atherothrombosis and/or plaque rupture)

The definition of the active agent to be used in claims 6 and 8 - 'purified subfraction of pooled immunoglobulin' is vague and unclear and not sufficiently disclosed, contrary to the requirements of Art. 5 and 6 PCT (see Section VIII). Due to this lack of clarity and disclosure, no comprehensive analysis of novelty and inventiveness is practicable at present.

It appears from the description that the subfraction according to claim 6 may by the one prepared by affinity purification based on binding to a phosphorylcholine conjugate, thus a subfraction comprising anti phosphorylcholie (aPC) antibodies (see page 7, paragraph 2). Novelty of claims 6,8 restricted to such subfraction would be anticipated by the disclosure of D9-D11 teaching atheroprotective effect of EO6/T15 - natural autoantibody to PC. If novelty of some of the claims over D9-D11 was to be acknowledged, the subject-matter

thereof would be considered to be obvious over these documents, thus to lack an inventive step.

Moreover, it is to be stressed that the application fails to provide any proof that the technical problem posed - provision of an agent to prevent atherothrombosis and/or plaque rupture - has actually been solved by any purified subfraction of pooled immunoglobulin. As the technical problem has not been solved, no inventiveness could be acknowledged

Claims 7,9 (pooled immunoglobulin for preventing atherothrombosis and/or plaque rupture)

The disclosure of D5 and D6 is still considered to be prejudicial to novelty of claims 7. D5 discloses use of intravenous immunoglobulin (Ivlg) for the treatment of non-viral and non-autoimmune induced heart disorders including coronary syndromes caused by a rupture of an atherosclerotic plaque in one of coronary arteries. D6 discloses immunomodulation including administration of Ivlg for treatment and prevention of atherosclerosis. Ivlg was found to be effective both during fatty streak and plaque formation of atherosclerosis.

It is to be stressed that treatment or prevention of atherosclerosis is considered to fall within the scope of prevention of atherothrombosis and or plaque rupture. When atherosclerosis is treated or prevented, formation or enlargement of atherosclerotic plaques is inhibited and/or reversed, thus there is a lower risk of atherothrombosis or plaque rupture. It appears that atherothrombosis and plaque rupture cannot occur without previous atherosclerosis, thus when atherosclerosis is treated, consequent atherothrombosis and plaque rupture is prevented. Moreover, no distinction can be made between the patient to be treated according to the present claims and those of D1 as patients in whom atherothrombosis and/or plaque rupture is to be prevented are prima facie patients having such plaques, i.e. atherosclerotic patients.

Claim 9 appears to be new but could not be considered inventive as being obvious in view of at least combination of D6 and D8 for the reasons stated above for claim 5.

Industrial applicability

Subject-matter of claims 1-3, 6, 7 is considered to be industrially applicable under Art. 33(1) and (4) PCT.

For the assessment of the present claims 4,5,8,9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application (clarity)

Claims 6,7 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined.

Claim 6 attempts to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. It is directed to the use of a purified subfraction of pooled immunoglobulin defined by the desirable function thereof, namely the ability thereof to inhibit antibodies binding to annexin V or to promote binding of annexin V to endothelium. Moreover, the agent itself is defined by the way of preparation thereof - as a subfraction purified for pooled immunoglobulin, no structural characteristic of the subfraction or fractionating method leading to said subfraction is defined, rendering the subject-matter further unclear. In order to perform the claimed invention, the skilled person would need to isolate all possible subfractions of pooled immunoglobulin and test them for their capacity to inhibit antibodies binding to annexin V, or to promote binding or annexin V to endothelium, which is considered as undue burden.

Although the claims cover almost unrestricted number of possible subfractions of pooled immunoglobulin with the capacity to inhibit antibodies binding to Annexin V or to promote binding of annexin V to endothelium, the application does not provide support for any such

serum subfraction. The only serum fraction which appear to be shown to increase binding of annexin to endothelium is the IgG-depleted plasma (see page 13, paragraphs 2, 3). No other subfraction increasing binding of annexin to endothelium are disclosed. No subfraction inhibiting antibodies binding to annexin V is shown by the application. In conclusion, the application does not provide sufficient information allowing a skilled person to perform the claimed invention over the whole scope claimed without undue burden, contrary to the requirements of Art. 5 and 6 PCT.

The term 'commercially available pooled immunoglobulin preparation' employed in claim 7 has no precise meaning as it is not internationally accepted as a standard descriptive term, thereby rendering the definition of the subject-matter of this claim unclear. In this respect, it my not be guaranteed that the product referred to does not have different composition when purchased from different producers or that the composition does not change with time.

Claim 9 is formulated as directed to a method or a use which renders the scope of protection sought unclear.